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K050029

510(k) Summary

PrognostiX *Cardio*MPO™ Test

This 510(k) summary is being submitted in accordance with the Safe Medical Devices Act of 1990 and 21 CFR 807.92.

General Information

Name and Address of Applicant:	PrognostiX, Inc. 10265 Carnegie Avenue Cleveland, OH 44106 216-445-7469 Thomas M. Jackson, Ph.D.
Date Prepared:	January 5, 2005
Device Trade Name:	*Cardio*MPO™ Test
Common Name:	Myeloperoxidase Test

Identification of Legally Marketed Device

diaDexus PLAC™ Test
510(k) number K030477
diaDexus, Inc.
343 Oyster Point Blvd.
South San Francisco, CA 94080

Intended Use

The *Cardio*MPO Test is an enzyme immunoassay intended for the quantitative determination of myeloperoxidase in human plasma, to be used in conjunction with clinical history, ECG and cardiac biomarkers to evaluate patients presenting with chest pain that are at risk for major adverse cardiac events, including myocardial infarction, need for revascularization, or death.

Device Description

The *Cardio*MPO Test is a sandwich enzyme immunoassay that uses two highly specific antibodies, one monoclonal and one polyclonal, and an enzyme labeled anti-rabbit IgG antibody for the measurement of MPO concentration in human plasma. The *Cardio*MPO Test is comprised of the *Cardio*MPO Reagent Kit, the *Cardio*MPO Calibrator Kit, and the *Cardio*MPO Control Kit.

The *Cardio*MPO Reagent Kit contains the following: a microtiter plate coated with a monoclonal anti-MPO antibody; a solution of primary polyclonal rabbit anti-MPO antibody; a solution of secondary goat anti-rabbit IgG antibody labeled with horseradish peroxidase solution; TMB substrate solution; Stop Solution; Wash Buffer Concentrate; Assay Buffer; and plate sealers.

The *Cardio*MPO Calibrator Kit contains six Calibrators comprised of human MPO in a phosphate-buffered matrix containing proteins, detergents, and stabilizers. Calibrators are intended to establish a calibration curve that is used to determine MPO concentration. Calibrator values are provided on individual Calibrator labels. Calibrators are provided ready-to-use.

The *Cardio*MPO Control Kit contains three Controls comprised of human MPO in a human plasma matrix. Controls are intended to monitor and evaluate the precision and accuracy of the *Cardio*MPO Test. Ranges are provided on individual Control labels. Controls are treated in the same manner as patient samples.

Calibrators are added directly to the appropriate wells of the Microtiter Plate. Assay Buffer is added to all wells that are intended for Control or sample analysis. Aliquots of Controls or samples are added to the appropriate wells and the plate is incubated for 60 minutes at 20-26°C. The wells are then washed with Wash Buffer to remove antigens not specifically bound to the immobilized antibody.

A yellow primary polyclonal rabbit anti-MPO antibody is added to each well and incubated for 60 minutes at 20-26°C. This antibody binds to the MPO captured on the plate. The plate is again washed with Wash Buffer to remove unbound primary antibody.

A blue secondary goat anti-rabbit IgG antibody, labeled with the enzyme horseradish peroxidase (HRP), is then added to each well and incubated for 30 minutes at 20-26°C. This antibody binds to the primary antibody, and the MPO in the sample is "sandwiched" between the monoclonal antibody on the solid phase and a complex of the rabbit anti-MPO and the HRP-goat anti-rabbit IgG antibody. The wells are washed with Wash Buffer to remove unbound HRP-labeled antibody.

The substrate, tetramethylbenzidine (TMB), is then added to each well and incubated for 10 minutes at 20-26°C resulting in the development of a blue color. Color development is stopped with the addition of Stop Solution, changing the color to yellow.

The enzymatic turnover of the substrate is determined spectrophotometrically at 450 nm, preferably with correction at 630 nm, and is directly proportional to the concentration of MPO. The absorbances of the Calibrators are used to plot a standard curve of absorbance versus MPO concentration from which the MPO concentration in the Controls or samples can be determined.

Comparison of New Device to Predicate Device

The chart below identifies the similarities and differences between the PrognostiX *Cardio*MPO Test and the predicate device, the diaDexus PLAC™ Test.

Characteristic	**PrognostiX *Cardio*MPO Test (Proposed)**	**diaDexus PLAC™ Test (K030477)**
Intended Use	Quantitative *in vitro* diagnostic test to detect myeloperoxidase in human plasma, to be used in conjunction with clinical history, ECG and cardiac biomarkers to evaluate patients presenting with chest pain that are at risk for major adverse cardiac events, including myocardial infarction, need for revascularization, or death.	Quantitative *in vitro* diagnostic test for the determination of Lp-PLA2 in human plasma, to be used in conjunction with clinical evaluation and patient risk assessment as an aid in predicting risk for coronary heart disease.
Analyte	Myeloperoxidase	Lipoprotein-associated phospholipase A2
Sample	Lithium Heparin Plasma	EDTA Plasma
Methodology	ELISA	ELISA
Detection Method	Optical Density at 450 nm	Optical Density at 450 nm
Risk to Patients	Minimal Risk	Minimal Risk
Laboratory Environment	Professional Laboratory	Professional Laboratory
Precision in plasma, Total Within-run	 <9% <6%	 <8% <6%
Interferences	No interference observed at the suggested NCCLS test concentrations of triglycerides, cholesterol, bilirubin, and albumin. No interference up to 1500 mg/L hemoglobin.	No interference observed at the suggested NCCLS test concentrations of hemoglobin, triglycerides, cholesterol, bilirubin, and albumin.
Clinical study results	Odds ratio increases from 1.0 to a max. of 5.2 across 4 quartiles	Risk ratio increases from 1.0 to a max. of 2.5 across 3 tertiles

Performance Characteristics

Sensitivity

The minimum detection limit, as calculated by interpolation of the mean plus two standard deviations of 24 replicates of the 0 pM MPO Calibrator (F), is 13 pM MPO.

Assay Precision

Total and within-run precision were determined by testing four Matrix Controls, containing human MPO in Calibrator matrix, and five Plasma Controls, containing human MPO in human lithium heparin plasma, with MPO concentrations distributed throughout the calibration range of the assay, according to NCCLS guidelines EP5-A. The nine samples were assayed in duplicate, using a single lot of reagents and Calibrators, on two separate plates per day, for twenty days. A new calibration curve was run in duplicate on each plate. Total precision in plasma samples was 8.2% and within-run precision was 5.5%.

Linearity

Lithium heparin plasma samples spiked to high MPO levels were intermixed with neat plasma samples with low MPO levels to create nine MPO concentrations across and exceeding the anticipated linear range. Linearity of the MPO levels measured in the mixtures was assessed using the polynomial evaluation of linearity as recommended in NCCLS guidelines EP6-A. The *Cardio*MPO Test was linear from 13 pM to 5223 pM MPO, within 60 pM or 9% in this interval.

Interfering Substances

The following substances, when tested in plasma containing 3000 pM and 1000 pM MPO, according to NCCLS guidelines EP7-A, were found not to interfere up to the concentrations indicated. Bias of 10% or less was not considered interference.

Substance tested	Test concentration (mg/L)	Comments
Acetylsalicylic acid	600	Toxic dose
Albumin	50000	High*
Amoxicillin	75	3x therapeutic dose
Bilirubin, conjugated	50	High*
Bilirubin, unconjugated	150	High*
Captopril	5	Toxic dose
Ceruloplasmin	600	High
Cholesterol	1000	High*
DNA	16.7	High
Fenofibrate	45	3x therapeutic dose
Hemoglobin	1500	Hemolysis**
Heparin, lithium	3000 U/L	3x therapeutic dose
Hydrochlorothiazide	6	3x therapeutic dose
Hydrocortisone	0.69	Toxic dose
Ibuprofen	500	Toxic dose
Indomethacin	36	2x therapeutic dose
Isosorbide dinitrate	0.15	3x therapeutic dose
Lovastatin	53	2x therapeutic dose
Methotrexate	160	Therapeutic dose
Metoprolol	5	Toxic dose
Naproxen	500	4x therapeutic dose
Niacin	0.5	5x therapeutic dose
Nifedipine	0.4	2x therapeutic dose
Salicylic acid	600	Toxic dose
Sodium azide	0.50%	5x preservative dose
Triglycerides	5000	Lipemia

* High level of interfering substance per NCCLS EP7-A

** Hemoglobin levels of 5000 mg/L produced a bias of >10%. A dose-response series showed a bias of <10% at <1500 mg/L hemoglobin within a 95% prediction interval.

Interfering Antibodies

Twenty-one plasma samples known to have elevated levels of heterophilic or other potentially interfering antibodies, such as HAMA, RF, anti-MPO p-ANCA, etc., were analyzed for interference in the *Cardio*MPO Test. The mean recovery of MPO from samples containing heterophilic antibodies was 108% with individual recoveries ranging from 89 to 118%. Therefore, no evidence of significant interference was observed due to the heterophilic antibodies tested in the *Cardio*MPO Test.

Cross-reactivity

The following potential cross-reactants, tested in both a plasma pool containing MPO and Assay Buffer according to NCCLS guidelines EP7-A, showed no significant cross-reaction in the assay up to the concentrations indicated.

Substance tested	Concentrations tested (nM)
α−1 antrypsin, human	1250, 125, 12.5
C-reactive protein, human	543, 54.3, 5.43
Lysozyme, human	4464, 446.4, 44.64
IgA, human	417, 41.7, 4.17
Elastase, human	2500, 250, 25
Lactoperoxidase, bovine	801, 80.1, 8.01
Lactoferrin, human	781, 78.1, 7.81
COX1, ovine	893, 89.3, 8.93
COX2, human	868, 86.8, 8.68
Thyroid peroxidase, human	595, 59.5, 5.95
Troponin I, human	2155, 215.5, 21.55

Spiking recovery

Fourteen lithium heparin plasma samples were spiked with 509.9, 1016, and 1500 pM MPO and analyzed for recovery. The percent recovery was calculated by dividing the mean measured MPO concentration of the spiked sample by the expected MPO concentration, where the expected MPO concentration was the sum of the measured MPO concentration in the neat plasma sample and the concentration of the MPO spike. The overall recovery of spiked MPO ranged from 89% to 105% with a mean of 97%.

Dilution recovery

Thirteen lithium heparin plasma samples were spiked with 1500 pM MPO and diluted 1:2, 1:4, 1:8, and 1:16 with Assay Buffer. The percent recovery was calculated by dividing the mean MPO concentration of the pre-diluted sample multiplied by the dilution factor by the mean MPO concentration of the sample with no pre-dilution. The mean recovery of a 1:2 dilution was 116%, with recoveries ranging from 102% to 131%. The mean recovery at dilutions of 1:4 through 1:16 rose from 132% to 145% due to decreased plasma matrix effects. The PrognostiX *Cardio*MPO Test is formulated to account for matrix effects associated with a 5 µL human plasma sample. PrognostiX does not recommend further dilution of samples. Samples with MPO levels exceeding the value of the highest Calibrator should be reported as greater than that level, e.g. > 5000 pM.

Hook Effect

There is no evidence of hook effect in the *Cardio*MPO Test up to 800,000 pM MPO, roughly 150 times greater than the upper end of the reportable range and 500 times greater than the median level of patients in the clinical study.

Reference Interval

Plasma samples from a population of apparently healthy blood donors, were evaluated with the *Cardio*MPO Test. A two-stage outlier detection scheme, a Box-Cox transformation followed by a robust outlier detection method, was used to eliminate six outliers. Since there was no significant difference in MPO levels between males (n=145) and females (n=149) after adjustment for outliers, the reference range was estimated from the adjusted normal subject population.

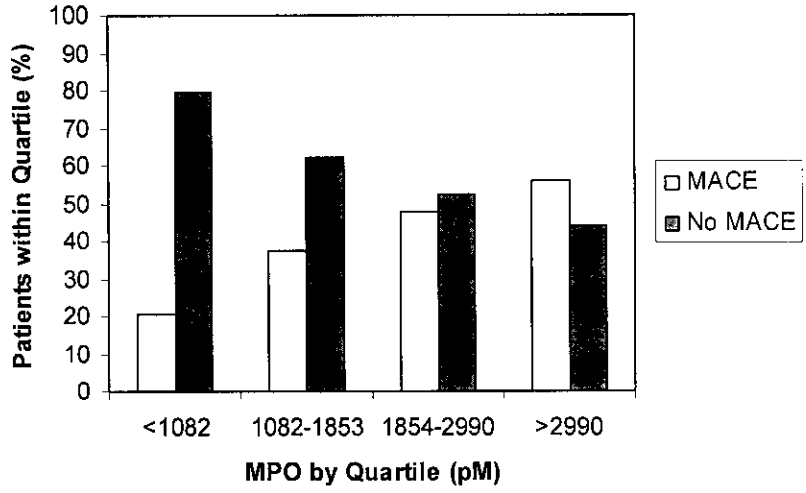
The median MPO level for subjects in the adjusted normal subject population was 193 pM and the range of results was 48 to 924 pM. The non-parametric distribution of myeloperoxidase levels in this normal population yields a two-tailed central 95% reference interval, corrected for the influence of outlier rejection, of 78 – 708 pM. However, in this application the more appropriate single-tailed lower 95% reference interval, again corrected for the influence of the outlier rejection method, is < 539 pM.

Summary of Clinical Study

To determine the efficacy of the PrognostiX *Cardio*MPO Test as a predictor of risk for major adverse cardiac events (MACE), MPO levels were measured in 560 banked plasma samples from a prior study of patients presenting to the Emergency Department within 24 hours of the onset of chest pain (Brennan, et al, N Engl J Med 2003; 349:1595-1604). Patients were followed for the development of myocardial infarction, need for revascularization, or death over the next 30-day and 6 month interval. Samples assayed with the PrognostiX *Cardio*MPO Kits were from patients aged 23 to 96 years. Median age was 64. The incidence of MACE was assessed by follow up phone calls at 30 days and 6 months.

Multivariate logistic-regression models (SAS version 8.0, SAS Institute) were developed to calculate odds ratios and 95% confidence intervals. The adjusted covariates were age, gender, race, Troponin T (≤0.03 ng/mL vs. >0.03 ng/mL) (McErlean et al. Am J Cardiol 2000;85:421-426), C-reactive Protein (<1 mg/L, 1-3 mg/L, >3 mg/L) (Brennan et al, N Engl J Med 2003;349:17,1595-1604), CK-MB (≤8.8 ng/mL vs. >8.8 ng/mL) (McErlean et al. Am J Cardiol 2000;85:421-426), history of smoking, history of diabetes, history of hypertension, and history of high cholesterol. Missing covariate information on some subjects reduced the study population. The risk of MACE in all patients in the ensuing 30-day period increased with increasing quartiles of myeloperoxidase levels. Adjusted odds ratios and the percentage of patients within an MPO quartile with and without MACE at 30 days are shown in the following graph and table.

Risk of MACE in All Patients

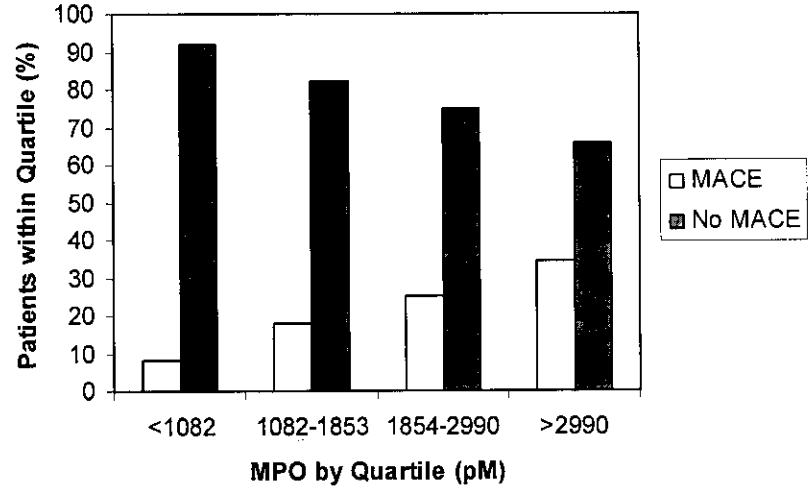


	MACE at 30 days, All Patients (n=523)			
MPO (pM)	**<1082**	**1082-1853**	**1854-2990**	**>2990**
Odds Ratio	1.0	2.5	2.8	3.3
95% CI	NA	1.3-4.8	1.5-5.6	1.7- 6.4
p value		p = 0.007	p = 0.0021	p < 0.001

*In each analysis the first quartile served as the reference group

Similar analysis of patients that were persistently negative for Troponin T (≤0.03 ng/mL) also revealed a significantly higher risk of MACE for patients with plasma MPO levels in higher quartiles.

Risk of MACE in Patients Persistently Negative for Troponin T



	MACE at 30 days, TnT negative Patients (n=304)			
MPO (pM)	**<1082**	**1082-1853**	**1854-2990**	**>2990**
Odds Ratio	1.0	3.4	4.1	6.9
95% CI	NA	1.2-9.4	1.5-11.4	2.5-19.2
p value		p = 0.0194	p =0.007	p < 0.001

*In each analysis the first quartile served as the reference group

It should be noted that different cut-off points may be appropriate for different clinical populations.

Conclusions

The PrognostiX *Cardio*MPO Test is acceptably precise, linear, accurate, and is not subject to appreciable cross-reactivity or interference. The detection limit of 13 pM is acceptable for the intended use of this test. The test is reproducible across several reagent lots, several instruments and multiple operators and should provide reliable and reproducible results when used by professional clinical laboratories.

The clinical evaluation of the *Cardio*MPO Test involved re-analysis of 560 banked lithium heparin plasma samples from an earlier study of patients with chest pain. The results of this study demonstrate that plasma levels of MPO are associated with risk of myocardial infarction, revascularization, and death. The performance testing and clinical data support the safety and effectiveness of the *Cardio*MPO Test as an aid in evaluating patients presenting with chest pain that are at risk for major adverse cardiac events, including myocardial infarction, need for revascularization, or death.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
2098 Gaither Road
Rockville MD 20850

MAY 10 2005

Thomas M Jackson, Ph.D.
Director of Product Development
Prognostix, Inc.
10265 Carnegie Avenue
Cleveland, OH 44106

Re: k050029
Trade/Device Name: *Cardio*MPO™ Test
Regulation Number: 21 CFR 866.5600
Regulation Name: Low- density lipoprotein immunological test system
Regulatory Class: Class II
Product Code: NTV, JJX, JIS
Dated: April 19, 2005
Received: April 20, 2005

Dear Dr. Jackson:

We have reviewed your Section 510(k) premarket notification of intent to market the device referenced above and have determined the device is substantially equivalent (for the indications for use stated in the enclosure) to legally marketed predicate devices marketed in interstate commerce prior to May 28, 1976, the enactment date of the Medical Device Amendments, or to devices that have been reclassified in accordance with the provisions of the Federal Food, Drug, and Cosmetic Act (Act) that do not require approval of a premarket approval application (PMA). You may, therefore, market the device, subject to the general controls provisions of the Act. The general controls provisions of the Act include requirements for annual registration, listing of devices, good manufacturing practice, labeling, and prohibitions against misbranding and adulteration.

If your device is classified (see above) into either class II (Special Controls) or class III (PMA), it may be subject to such additional controls. Existing major regulations affecting your device can be found in Title 21, Code of Federal Regulations (CFR), Parts 800 to 895. In addition, FDA may publish further announcements concerning your device in the Federal Register.

Please be advised that FDA's issuance of a substantial equivalence determination does not mean that FDA has made a determination that your device complies with other requirements of the Act or any Federal statutes and regulations administered by other Federal agencies. You must comply with all the Act's requirements, including, but not limited to: registration and listing (21 CFR Part 807); labeling (21 CFR Parts 801 and 809); and good manufacturing practice requirements as set forth in the quality systems (QS) regulation (21 CFR Part 820).

This letter will allow you to begin marketing your device as described in your Section 510(k) premarket notification. The FDA finding of substantial equivalence of your device to a legally marketed predicate device results in a classification for your device and thus, permits your device to proceed to the market.

If you desire specific information about the application of labeling requirements to your device, or questions on the promotion and advertising of your device, please contact the Office of *In Vitro* Diagnostic Device Evaluation and Safety at (240)276-0484. Also, please note the regulation entitled, "Misbranding by reference to premarket notification" (21CFR Part 807.97). You may obtain other general information on your responsibilities under the Act from the Division of Small Manufacturers, International and Consumer Assistance at its toll-free number (800) 638-2041 or (301) 443-6597 or at its Internet address http://www.fda.gov/cdrh/industry/support/index.html

Sincerely yours,

Jean M. Cooper MS, DVM

Jean M. Cooper, MS, D.V.M.
Director
Division of Chemistry and Toxicology
Office of *In Vitro* Diagnostic Device
Evaluation and Safety
Center for Devices and
Radiological Health

Enclosure

Indications for Use

510(k) Number (if known): K050029

Device Name: *Cardio*MPO™ Test

Indications for Use:

The *Cardio*MPO™ Test is comprised of the *Cardio*MPO Reagent Kit, the *Cardio*MPO Calibrator Kit, and the *Cardio*MPO Control Kit.

The *Cardio*MPO Reagent Kit is an enzyme immunoassay intended for the quantitative determination of myeloperoxidase in human plasma, to be used in conjunction with clinical history, ECG and cardiac biomarkers to evaluate patients presenting with chest pain that are at risk for major adverse cardiac events, including myocardial infarction, need for revascularization, or death.

The PrognostiX *Cardio*MPO Calibrator Kit is intended for use with the *Cardio*MPO Reagent Kit to establish a calibration curve that is used to determine MPO concentration.

The PrognostiX *Cardio*MPO Control Kit is intended for use with the *Cardio*MPO Reagent Kit as an assayed quality control sample to monitor and evaluate the precision and accuracy of the *Cardio*MPO Test.

Prescription Use X AND/OR Over-the-Counter Use _____
(Part 21 CFR 801 Subpart D) (21 CFR 807 Subpart C)

(PLEASE DO NOT WRITE BELOW THIS LINE-CONTINUE ON ANOTHER PAGE IF NEEDED)

Concurrence of CDRH, Office of In Vitro Diagnostic Device Evaluation and Safety (OIVD)

Carol C Benson

Division Sign-Off

Office of In Vitro Diagnostic
Device Evaluation and Safety

510(k) K050029

Submitted on: 05 January 2005